

A robust R&D project portfolio optimization model for pharmaceutical contract research organizations

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Abstract:

Pharmaceutical drug Research and Development (R&D) outsourcing to contract research organizations (CROs) has experienced a significant growth in recent decades and the trend is expected to continue. A key question for CROs and firms in similar environments is which projects should be included in the firm's portfolio of projects. As a distinctive contribution to the literature this paper develops and evaluates a business support tool to help a CRO decide on clinical R&D project opportunities and revise its portfolio of R&D projects given the existing constraints, and financial and resource capabilities. A new mathematical programming model in the form of a capital budgeting problem is developed to help revising and rescheduling of the project portfolio. The uncertainty of pharmaceutical R&D cost estimates in drug development stages is captured to mimic a more realistic representation of pharmaceutical R&D projects, and a robust optimization approach is used to tackle the uncertain formulation. An illustrative example is presented to demonstrate the proposed approach.

Keywords: Pharmaceutical contract research organization (CRO) | Research and Development (R&D) | Project selection and scheduling | Uncertainty | Robust optimization

Article:

1. Introduction

Americans spent over \$2.6 trillion on healthcare last year. This represents about 17.9% of the total US GDP. The World Health Organization estimates that the healthcare share of US GDP could climb to 34% by 2040 and warns of adverse consequences for the world economy if the current cost trajectory is not corrected. A closer look at the healthcare expenditure shows that pharmaceuticals accounts for over 12.9% of total expenditure and it is projected to be the fastest growing portion of healthcare spending. This is due to high prices of prescription drugs, particularly brand name and specialty drugs, and rising costs associated with the Research and Development (R&D) of new drugs (CMS Report, 2011). The pharmaceutical industry has long argued that the process of drug discovery through R&D is very expensive and requires substantial capital expenditure. For example, an average cancer drug costs around \$1.75 billion to research and develop and may take up to 10 years to test and market. In 2008, American pharmaceutical companies spent over \$45 billion on developing new drugs or modifying existing drugs. According to the Science and Engineering Indicators 2012 report published by the National Science Foundation, pharmaceuticals and medicines are the highest R&D intensive industries in the world after semiconductor and communication industries. The average R&D intensity in the pharmaceutical industry—the ratio of total R&D spending to total sales revenue—is 12.2%, which is more than three times that of the average manufacturing firm in the US.

R&D expenditures in the pharmaceutical industry might be as high as 40% of the cost of a newly developed drug (Gassmann et al., 2008). A significant contributor to the high R&D costs in pharmaceutical drug development projects is the high prevalence of technological and market uncertainties (Rogers et al., 2002). Technological uncertainties are related to the efficacy and safety of the drugs being developed while market uncertainties are related to the supply and demand factors in the marketplace. Despite these uncertainties, pharmaceutical companies have increasingly grown their expenditures on R&D in an effort to boost profitability through the introduction of novel drugs for treatment of various ailments (Lowman et al., 2012). This rising expenditure in pharmaceutical R&D projects is due to increases in cost of discovering new drugs, as well as higher costs associated with conducting clinical trials for developing these drugs. It is also important to note that recently discovered drugs with demonstrated higher levels of sophistication may require an even more costly and time-consuming clinical trial phases to ensure their safety and efficacy before they could be introduced to the market (Craig and Malek, 1995 and DiMasi and Grabowski, 2007).

As shown in Fig. 1, pharmaceutical drug development pipeline includes drug discovery, pre-clinical and clinical trials, FDA review, and production and marketing phases. Among these development phases, clinical trials are the most time-consuming and investment-intensive ones. Clinical trials take about 6 years to complete and represent more than 50% of total pharmaceutical R&D spending (Zeller, 2002, Mirowski and Van Horn, 2005 and Parexel, 2004).

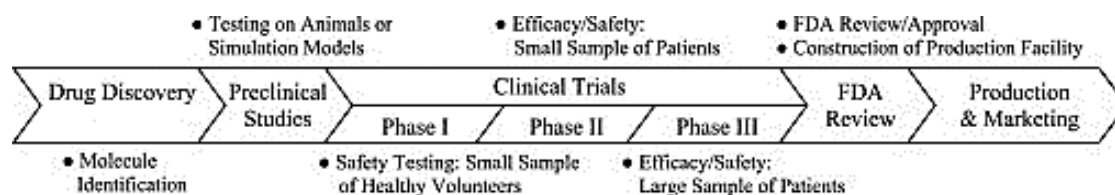


Fig. 1. Pharmaceutical drug development pipeline.

Given the cost and complexities associated with developing new drugs, pharmaceutical companies typically outsource some of their drug development activities to specialized organizations in order to better focus on their own core competencies. These specialized organizations are referred to as contract research organizations (CROs). CROs were “born” in the late 1970s and quickly assumed a significant role in the pharmaceutical industry in order to help the industry balance the need to consolidate its operations while simultaneously address getting drugs quickly through the development pipeline (Piachaud, 2002). The Association of Clinical Research Organizations (ACRO) estimates that over 46% of pharmaceuticals have outsourced their R&D projects to CROs. ACRO also estimates that CROs employ over 2 million people and are present in 115 countries (ACRO, 2013). The CRO industry represents over 33% of the total spending on pharmaceutical R&D (Lowman et al., 2012). It is estimated that in the near future, CRO’s share of total pharmaceutical R&D will exceed 60% (ACRO, 2013). The leading CROs manage more than 45,000 clinical trials annually with revenues in excess of \$20 billion (Milne and Paquette, 2004, Tufts Center, 2006a and Getz, 2007). The CRO industry is also very concentrated; the top 10 out of existing 1000 CROs in the global market control more than 80% of the total market share (Shuchman, 2007 and Getz, 2007). This indicates that the CRO market consists of a few big multinational companies with R&D departments even larger than some of their pharmaceutical clients along with numerous small or medium sized companies with a niche in national or regional markets (Piachaud, 2002).

The CRO market has expanded from drug discovery and preclinical work to clinical trials, drug manufacturing, and even marketing (Tufts Center, 2006b and Mehta and Peters, 2007). While it seems that it is the increase in the quantity of R&D projects that has promoted the need to outsource clinical trials, there are basically other motivations for pharmaceutical companies to use more outsourcing (Piachaud, 2002). These include higher cost efficiency (Huang et al., 2009), less time to market (Mahnke et al., 2006), increased opportunity to gain needed knowledge, availability of advanced skills and technologies (Coombs et al., 2003), and the increased globalization of drug development (Gassmann et al., 2010). The CRO of today is a key driver of drug development success (Lowman et al., 2012).

Although the practice of drug development outsourcing to CRO has been the motivation of numerous researchers (Alexander and Young, 1996, Rettig, 2000, Dickert et al., 2002, Piachaud, 2002, Quelin and Duhamel, 2003, Mirowski and Van Horn, 2005, Angell, 2008, Hsuan and Mahnke, 2011 and Zirpoli and Becker, 2011), the majority of conducted studies are descriptive in nature and have been studied from the perspective of the goal attainment for the

pharmaceutical companies and not for the CROs. Within the pharmaceutical business, for example, short time to market increases the novelty of a potential blockbuster drug to achieve a prolonged competitive advantage (Arlington, 1997 and Piachaud, 2002). A prolonged clinical testing may significantly reduce the commercial value of a drug or may even render the whole project infeasible (Bauer and Fischer, 2000). In fact, studies show that financial and commercial reasons account for more than one third of research abandonment which often occurs during late clinical testing phases (DiMasi, 2001). Thus, the role of the CRO is very critical in achieving the drug development goals of client organizations. A 2010 survey of about 400 drug manufacturers and biotech companies showed a potential growth of about 4-8% in CRO R&D budgets, indicating that the number of outsourcing activities is on the upward trend. Given this trend, the question that needs to be asked is whether CROs have the ability to absorb all the demand from client organizations. And if they do not, how should they balance their capabilities with the contract project loads in order to sustain long term profitability and growth? In other words, CROs must decide on which R&D projects to include in their optimum mix of project portfolio given their capacity constraints and profitability goals. Selecting a wrong mix of projects not only adversely impacts the contractual and financial obligations, but may also reduce the ability to successfully execute other projects already in the portfolio.

Realizing this necessity, the goal of this paper is to develop a business support tool to help CROs make their contract decisions effectively by integrating project opportunities with existing technical, financial, and resource restrictions within a mathematical model. There is very limited research on CROs in this context. The closest body of literature that underpins such models is referred to as the project selection and scheduling (PSS). Since the PSS literature is developed for generic projects, we need to modify the problem definition to account for pharmaceutical R&D projects as a special category of R&D projects. From a modeling perspective, the distinguishing characteristics of R&D projects from those of generic projects occur on the highly uncertain nature of R&D projects in that R&D cost and revenue estimates are very unreliable and the market outcome is very risky (DiMasi, 2001). To account for this uncertainty we employ a recently developed approach, called robust optimization, to solve our formulated model for pharmaceutical R&D project portfolio decision making.

The remainder of this paper is organized as follows. In the next section, we review the PSS literature, introduce the robust optimization concept, review its recent applications in project selection and project scheduling, and discuss its relevance to R&D PSS. In Section 3, we formally define the problem and propose our nominal model. Section 4 is dedicated to the introduction of a robust optimization framework and formulation of the robust counterpart model. In Section 5, we present the results of our robust CRO portfolio optimization approach using an illustrative example. Finally, Section 6 provides some managerial implications along with the conclusions.

2. Literature review

In the project management literature, project decision is usually considered the same as the project selection. As a result, the majority of studies generally do not include project scheduling as part of the decision process (Coffin and Taylor, 1996). As such, most of these studies present models that are usually designed to select a subset of projects from a larger pool of candidate projects to meet return objectives and budget constraints (Fox et al., 1984). In addition, these models sometimes consider resource allocation (Taylor et al., 1982) and project risk (Heidenberger, 1996 and Gabriel et al., 2006) in the selection process. Project scheduling becomes a subsequent follow-up activity after the selection process.

There are a few mathematical models that include the scheduling aspect of projects as part of the decision process. The resulting PSS problem can be classified into two different categories. In the first category each project is composed of a set of tasks requiring specific resources to complete, and precedence relations among tasks (within a project or between projects) exist. The major focus of this category is on the scheduling aspect of tasks, and the proposed models and solution techniques are similar to what is generally referred to as the resource constrained project scheduling problem (Coffin and Taylor, 1996, Kolisch and Hartmann, 2006 and Chen and Askin, 2009). In the second category it is assumed that each project is composed of a set of stages which, upon selection of the project, must be sequentially accomplished. The major focus of this category is on selection rather than scheduling of projects.

The first notable work in the second category, which is pertinent to R&D projects and hence our problem, is presented in Ghasemzadeh et al. (1999) where a multiobjective binary integer linear model with additive objectives is developed. They consider resource limitations and interdependences among projects and comment on the issue of sensitivity of the resulting portfolio to problem parameters. To address the scheduling problem resulting from the uncertainty in parameters, they re-optimize the model for sensitive parameter values through an interactive process. Benli and Yavuz (2002) address this problem differently by presenting a binary integer linear model where total net present value of selected projects is maximized and capital budgets and precedence relations among projects are considered. Sefair and Medaglia (2005) extend this work by incorporating exogenous cash flow generation and considering risk minimization as the second objective function. Zuluaga et al. (2007) extend Sefair and Medaglia (2005) by considering budget and benefit interdependence among projects, but do not consider the second objective of risk minimization. Sun and Ma (2005) address this problem within the R&D setting of a company and attempt to find a solution that maximizes the total priority of projects while budget restrictions in future time periods are respected. They formulate the problem as a simple packing multiple boxes model and heuristically solve it in a sequence of binary integer linear (Knapsack) models. Medaglia et al. (2008) address the selection and scheduling of public sector projects subject to resource limitations and precedence constraints, where endogenous project cash flow generations in addition to exogenous budgetary limits exist. They develop a multiobjective mixed integer linear programming (MILP) model with additive objectives and perform sensitivity analysis on various problem parameters. They also accentuate

the issue of solution robustness and illustrate how robustness may be used as a negotiation tool in a political environment. Carazo et al. (2010) develop a multiobjective nonlinear binary integer model to select and schedule a project portfolio where all problem data are deterministic, and resource constraints, project interdependence, and the possibility of transferring resources to the following period are taken into account. They assume no *a priori* information on the objectives' preferences and propose a metaheuristic procedure based on scatter search to determine the set of (Pareto) efficient portfolios.

It is worth noting that previous studies have addressed the PSS problem from a deterministic point of view. Some studies (e.g. Ghasemzadeh et al., 1999 and Medaglia et al., 2008) have commented on the uncertainty of parameters and used sensitivity analysis to investigate the stability of the solutions with regard to uncertainty in the data. We emphasize that sensitivity analysis, as a *post-optimization* tool, measures sensitivity of the solution only regarding small changes in the problem data and does not measure the amount by which the solution can violate constraints of the problem. In addition, while sensitivity analysis quantifies local stability of the solution with respect to small data changes, it does not provide a tool to improve this stability. Finally, sensitivity analysis requires the analysis of uncertain parameters one at a time.

Robust optimization is a new approach that addresses uncertainty of all problem parameters concurrently. It guarantees feasibility and optimality of the solution for the worst instances of the problem without jeopardizing performance of the optimal solution. Robust optimization incorporates the random character of problem parameters without making any assumptions about their probability distributions. The use of robust optimization to address data uncertainty of pharmaceutical R&D project is pertinent because development of drugs precludes the availability of historical data to simulate the probability or possibility distribution of the R&D project parameters. As a result, the application of fuzzy or stochastic optimization approaches to pharmaceutical R&D that deals with unexperienced uncertainties is questionable. Both fuzzy and stochastic approaches assume that possible outcomes of an event and their distributions are known with certainty. While in robust optimization the possible outcomes are known, no distribution is associated with them. In addition, fuzzy or stochastic optimization approaches optimize the objective function based on the preference degree of the decision maker whereas robust optimization seeks a solution that remains *reasonably good* under all possible realizations of the uncertain parameters.

Robust optimization was first introduced by Soyster (1973). In his approach each uncertain parameter is considered at its worst possible value within a range, resulting in solutions that are overly conservative. El-Ghaoui et al. (1998) and Ben-Tal and Nemirovski (2002) took the next steps by addressing the overconservatism issue and considered ellipsoidal uncertainties which result in conic quadratic robust counterparts for uncertain linear formulations. Although these formulations are able to approximate more complicated uncertainty sets they lead to counterpart models that are nonlinear and hence, computationally less tractable and less practical than linear models. Bertsimas and Sim (2003) developed the “budget of uncertainty” approach that has the

advantage of retaining linearity over the robust counterpart. In addition, this approach provides full control over the degree of conservatism for every constraint.

A recent review by Gabrel et al. (2014) reveals that although there are a number of studies that present the application of robust optimization in the context of either project selection or project scheduling, no such application exists in the PSS domain. In the context of project selection, Liesiö et al. (2008) developed a multiobjective project selection model where a wide range of project interdependences and variable budget levels exist. They considered incomplete information on project costs and used an algorithm to determine all non-dominated solutions. Driouchi et al. (2009) provided a robustness framework for monitoring real options under uncertainty that can be used to make robust project decisions. Hassanzadeh and Modarres (2009) used the real options approach to value R&D projects and developed a model to select a robust portfolio of R&D projects. Düzgün and Thiele (2010) considered a project selection problem where uncertainty in project cash flow depends on an underlying random variable. They modeled the uncertainty using multiple ranges for each uncertain parameter and developed a mathematical optimization model as well as a ranking heuristic to find the best portfolio of R&D projects. Hassanzadeh et al. (2014) considered a multiobjective R&D project portfolio selection problem where benefits and costs are uncertain. They used the budget of uncertainty approach within an interactive Tchebycheff procedure to elicit preference information from the decision maker and find the preferred portfolio of projects. Lo Nigro et al. (2014) developed a biopharmaceutical R&D project selection model where future cash inflows of successfully completed projects can be used to partially fund the development stages of other ongoing projects. They allowed for the option to develop a project either internally or through allies and used the real options valuation approach to evaluate candidate projects. Their proposed model maximizes the real options value of the portfolio less discounted value of the endogenous cash flows used to fund other projects. In the context of project scheduling Yamashita et al. (2007) considered a formulation of project scheduling problem with resource availability cost where uncertainty in activity durations is modeled as a set of scenarios, and a heuristic based on scatter search is proposed to solve the formulation. Artigues et al. (2013) also considered a project scheduling problem with uncertain activity durations. They formulated the problem as a minimax-regret optimization model and used a scenario-relaxation algorithm to solve the problem. They also commented on the computational intractability of their approach even for medium-sized instances of the problem and proposed a heuristic solution procedure which demands less CPU time.

In this paper, we develop a mathematical model to periodically select and concurrently schedule a portfolio of R&D projects. Our contribution is that our proposed model and solution approach account for the critical distinctions between R&D project and generic project setting. First, early market introduction is a significant factor in commercial success of an R&D project (Arlington, 1997 and Piachaud, 2002); it has the short-term benefit of higher profits (Musselwhite, 1990) as well as long-term benefit of higher market share (Robinson and Fornell, 1985) and more

profitable drug life cycle (Bauer and Fischer, 2000). Therefore, R&D project returns (contract values) are highly time-dependent. Second, R&D projects are very risky and hence, externally available funds for investment have much higher cost than internally available funds (Grabowski and Vernon, 2000). This is in addition to transaction costs, tax advantages, financial distress costs, and asymmetric information that make externally available funds generally more expensive than internally available funds (Hubbard, 1998). Our formulated model allows for reinvestment of revenues generated from successfully delivered R&D projects as an alternative to borrowing from a financial institution. Third, R&D projects usually have long life cycles and are very imprecise and uncertain in terms of cash flow estimates compared to non-R&D projects (Carlsson et al., 2007). To address this issue, we employ the robust optimization method of Bertsimas and Sim (2003) as our solution approach to account for this inherent uncertainty in R&D financial estimates.

3. Problem definition

In order to characterize the problem, consider a situation where a CRO faces several R&D project opportunities from various pharmaceutical companies. Each project opportunity, if undertaken, will lead to a return equal to the contract value of the project. Without loss of generality, we assume that this revenue occurs as soon as the project is completed. In addition to new project opportunities, we assume that the CRO is currently conducting a portfolio of ongoing R&D projects where each project is undergoing a particular clinical testing phase. So, the problem that needs to be addressed is which ongoing projects should be abandoned, which additional project(s) should be accepted into the portfolio, and how should the new portfolio mix be scheduled.

Every R&D project has a specific number of development phases, each of which requires specific financial as well as human, laboratory, and several other resources. Due to the limited availability of these resources, the CRO cannot initiate all promising projects simultaneously. The CRO, however, may offer a delayed initiation to the pharmaceutical company which will highly degrade the contract value. To formally define the problem, we first observe that a clinical testing phase may span several time periods. To model clinical trials we consider that each phase consists of several project stages where each stage lasts for a single time period, e.g. one year. We focus on this problem over a planning horizon of T time periods. The CRO cash flows are modeled as financial transactions between the CRO and a bank. Outflows include costs to be paid for drug development purposes and inflows involve external budgets and revenues received as a result of delivering a completed drug project to the client, as shown in Fig. 2.

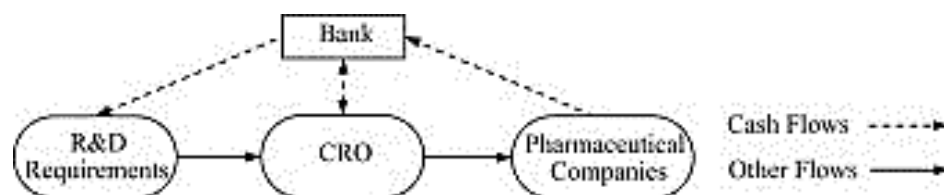


Fig. 2. Flows in the problem setting.

Our proposed R&D PSS model encompasses the following parameters:

n	number of projects (ongoing and candidate)
k_i	duration of project i in terms of stages or periods (project life)
t_i^-	early start time of project i
t_i^+	tardy start time of project i ($t_i^- \leq t_i^+$)
c_{it}^k	time-dependent cost of undertaking the k th stage of project i in period t ($k \leq k_i$)
$-c_{it}^{k_i+1}$	contract value of project i if completed at the beginning of period t
r_{im}^k	amount of resource type m required to handle k th stage of project i
r_t	single-period interest rate in period t
Δ	premium paid over the interest rate for single-period borrowing; strictly positive
β_t	external budget available in period t
B	liability (borrowing) limit
R_t^m	amount of resource type m available in period t
T	planning horizon (in time periods)
g_{ip}	precedence gap between project i and project p

the following sets:

Ω	set of precedence relations
Θ^M	set of mandatory projects
$OO\Theta$	set of ongoing projects that should not be interrupted

and the following decision variables:

l_t

amount of cash in account at the beginning of period t (earning interest at rate r_t)

b_t

total liability at the beginning of period t (with interest rate $r_t + \Delta$)

$$x_{it} = \begin{cases} 1 & \text{if project } i \text{ is initiated at the beginning of period } t \\ 0 & \text{otherwise} \end{cases}$$

In addition, we define possible precedence relations in the following sense: if project i precedes project p , then $(i, p) \in \Omega$ and their precedence gap is an integer number, *i.e.* $g_{ip} \in \mathbb{Z}$. If $g_{ip} = 0$, then project i must be over before project p can begin; if $g_{ip} < 0$, an overlap of at most $(-g_{ip})$ periods is allowed; finally, if $g_{ip} > 0$, project i must be over at least g_{ip} periods before project p can begin. We also view every ongoing project as a new project opportunity with the related parameters modified accordingly. In addition, without loss of generality, we assume that financial transactions, cost spending, and resource consumptions occur at the beginning of periods. The nominal R&D PSS problem is formulated similar to a capital budgeting problem as

equation(1)

$$\begin{aligned} & \max (l_{T+1} - b_{T+1}) \\ & s.t. \end{aligned}$$

equation(2)

$$\begin{aligned} & \sum_i \sum_{j = \max\{t_i^-, t - k_i\}}^{\min\{t, t_i^+\}} c_{it}^{t-j+1} x_{ij} + l_t + b_{t-1}(1 + r_{t-1} + \Delta) \\ & \leq l_{t-1}(1 + r_{t-1}) + b_t + \beta_t, \quad t = 1, \dots, T+1 \end{aligned}$$

equation(3)

$$\sum_{j = t_i^-}^{t_i^+} x_{ij} \leq 1, \quad i = 1, \dots, n$$

equation(4)

$$\sum_i \sum_{j = \max\{t_i^-, t - k_i + 1\}}^{\min\{t, t_i^+\}} r_{im}^{t-j+1} x_{ij} \leq R_t^m \quad \forall m; \quad t = 1, \dots, T$$

equation(5)

$$x_{pt} \leq \sum_{j = t_i^-}^{\min\{t_i^+, t - k_i - g_{ip}\}} x_{ij}, \quad (i, p) \in \Omega; \quad t = t_p^-, \dots, t_p^+$$

equation(6)

$$\sum_{j = t_i^-}^{t_i^+} x_{ij} = 1, \quad i \in \Theta^M$$

equation(7)

$$x_{i1} = 1, \quad i \in \Theta^0$$

equation(8)

$$b_t \leq B, \quad t = 1, \dots, T$$

equation(9)

$$x_{ij} \in (0, 1), \quad i = 1, \dots, n; j = t_i^-, \dots, t_i^+$$

equation(10)

$$b_t, l_t \geq 0, \quad t = 1, \dots, T+1.$$

The bank account periodically receives cash from completed projects and potential external budgets in order to finance the ongoing projects. At the beginning of period t , the account gains interest $r_t l_t$, pays interest $(r_t + \Delta) b_t$, and rolls over to the next period. The bank account balance at the beginning of period t , represented by $l_t - b_t$, encompasses all revenues gained from completed project, investment costs paid to undertake project phases, and interests gained from or paid to the bank up to period t (apparently, $l_t b_t = 0$ for all t). We therefore formulate the objective function (1) to maximize the account balance at the end of the planning horizon T . The cash balance constraint is shown in (2), where cash in period t comes from the principal and interest from lending in period $t-1$, the amount borrowed in period t , and exogenous budget in period t . Cash is spent on lending in period t , the principal plus interest related to the amount borrowed in period $t-1$ at rate $(r_{t-1} + \Delta)$, and the cost of undertaking stage $t-j+1$ of projects initiated at time period j . Note that we have chosen $c_{it}^{k+1} < 0$ as the negative contract value merely to simplify the writing of this equation. Constraint (3) ensures that each R&D project, if selected, starts only once during the planning horizon. Constraint set (4) is established for each renewable resource, such as staff and laboratory to ensure that each resource type consumption remains within the available resource level of each period. Constraint (5) presents technical interdependence between projects; if $x_{pt}=1$ and project i is the predecessor of project p , then project i must start no earlier than t_i^- and no later than $\min \{t_i^+, t - k_i - g_{ip}\}$. Mandatory projects may also exist in the portfolio decision process. These are projects that, based on certain considerations, must be definitely included in the portfolio. Constraint set (6) guarantees the inclusion of these projects in the portfolio. Moreover, at periodic revisions of the portfolio, it is normal for many or all of the ongoing projects to be continued. Constraint set (7) does not allow such ongoing projects to be interrupted. Constraint set (8) specifies the liability limit in each period. Finally, constraints (9) and (10) identify decision variables of the problem. In the next section, we show how to incorporate the uncertainty of R&D financial estimates in the above formulation.

4. Robust CRO portfolio optimization model (RoCROP)

4.1. Robust optimization for uncertain linear programming problems

Consider the following MILP problem:

equation(Model 1)

$$\begin{aligned} \max \quad & \sum_j c_j x_j \\ \text{s.t.} \quad & \sum_j a_{ij} x_j \leq b_i, \quad i = 1, \dots, m \\ & l_j^L \leq x_j \leq l_j^U, \quad j = 1, \dots, n \\ & x_j \in \mathbb{Z}, \quad j = 1, \dots, n' \end{aligned}$$

The problem has n decision variables (x_j), the first n' of which are integral. c_j , a_{ij} , and b_i are objective function coefficients, technical coefficients, and right-hand side values, and l_j^L and l_j^U are lower and upper bounds on decision variables, respectively. Without any loss of generality, we assume that data uncertainty affects only a_{ij} (Bertsimas and Sim, 2003). To capture uncertainty we only assume that each a_{ij} is known to belong to an interval that is centered at the nominal value \bar{a}_{ij} and has half-interval length of \hat{a}_{ij} , i.e. $a_{ij} \in [\bar{a}_{ij} - \hat{a}_{ij}, \bar{a}_{ij} + \hat{a}_{ij}]$ and no distribution is associated with the uncertain parameter in its support. As much as it is unlikely that all coefficients are equal to their nominal value, it is also unlikely that they are all equal to their worst-case value. For this reason, the “safest” approach where all parameters are taken equal to their worst bound leads to severe deterioration of the objective function without necessarily being justified in practice. Hence, the conservatism degree of the solution needs to be appropriately adjusted so that a reasonable trade-off between robustness and performance is achieved.

To quantify this concept in mathematical terms, the absolute value of the scaled deviation of parameter a_{ij} from its nominal value is defined as $z_{ij} = |a_{ij} - \bar{a}_{ij}| / \hat{a}_{ij}$. Obviously, z_{ij} takes values in interval $[0, 1]$. We now impose a *budget of uncertainty* in the following sense: the total absolute value of the scaled deviation of the parameters in the i th constraint cannot exceed some, not necessarily integer, threshold Γ_i , i.e. $\sum_{j=1}^n z_{ij} \leq \Gamma_i \quad \forall i$. By taking $\Gamma_i=0$ ($\Gamma_i=n$) we obtain the nominal (worst) case formulations. Bertsimas and Sim, 2003 and Bertsimas and Sim, 2004 show that letting the threshold Γ_i vary in $(0, n)$ makes it possible to build a robust model with greater flexibility without excessively affecting the optimal objective function. Intuitively, the budget of uncertainty rules out large deviations in $\sum_j a_{ij} x_j$ which plays a predominant role in worst-case analysis but actually occurs with negligible probability. In mathematical terms, let

$$\Lambda = \{a_{ij} \in [\bar{a}_{ij} - \hat{a}_{ij}, \bar{a}_{ij} + \hat{a}_{ij}], \quad \sum_{j=1}^n z_{ij} \leq \Gamma_i \quad \forall i\}.$$

The robust problem is then formulated as

equation(Model 2)

$$\begin{aligned}
 & \max \sum_j c_j x_j \\
 & \text{s.t.} \quad \sum_j a_{ij} x_j \leq b_i, \quad i = 1, \dots, m; \quad a_{ij} \in \Lambda \\
 & \quad \quad l_j^L \leq x_j \leq l_j^U, \quad j = 1, \dots, n \\
 & \quad \quad x_j \in \mathbb{Z}, \quad j = 1, \dots, n'
 \end{aligned}$$

Bertsimas and Sim (2003) prove that uncertain linear programming Model (2) has the following robust, linear counterpart:

equation(Model 3)

$$\begin{aligned}
 & \max \sum_j c_j x_j \\
 & \text{s.t.} \quad \sum_j \bar{a}_{ij} x_j + \Gamma_i q_i + \sum_j r_{ij} \leq b_i, \quad i = 1, \dots, m \\
 & \quad \quad q_i + r_{ij} \geq \hat{a}_{ij} y_j, \quad i = 1, \dots, m; j = 1, \dots, n \\
 & \quad \quad -y_j \leq x_j \leq y_j, \quad j = 1, \dots, n \\
 & \quad \quad l_j^L \leq x_j \leq l_j^U, \quad j = 1, \dots, n \\
 & \quad \quad x_j \in \mathbb{Z}, \quad j = 1, \dots, n' \\
 & \quad \quad q_i, r_{ij}, y_j \geq 0, \quad i = 1, \dots, m; j = 1, \dots, n
 \end{aligned}$$

In the above model, the latent variables q_i and r_{ij} have no particular meaning but together with y_j determine the amount by which uncertain parameter a_{ij} deviates around \bar{a}_{ij} . The above counterpart is of the same class as the nominal problem, that is, a MILP problem. This is a highly attractive feature of this approach since such programming problems can be solved by standard optimization packages. Another interesting property of this approach is that even if the total realized deviation of the uncertain parameters in constraint i is more than Γ_i , the robust solution will still be feasible with very high probability.

4.2. Robust counterpart of nominal R&D PSS model

In real world applications, it is the uncertainty of R&D cost estimates that substantially affects the portfolio decision. Therefore, without loss of generality, we consider that uncertainty merely affects cost estimates of drug development phases. To tackle the nominal formulation, we model uncertain cost estimates by assuming that each uncertain c_{it}^k belongs to an interval centered at its nominal value \bar{c}_{it}^k and of half-length \hat{c}_{it}^k but its exact value is unknown. We define the absolute value of the scaled deviation of each uncertain cost estimate from its nominal value

as $\eta_{it}^k = |c_{it}^k - \bar{c}_{it}^k| / \hat{c}_{it}^k$, and add the following constraint to (1), (2), (3), (4), (5), (6), (7), (8), (9) and (10):

equation(11)

$$\sum_i \sum_{j = \max\{t_1^-, t - k_i\}}^{\min\{t, t_i^+\}} \eta_{it}^{t-j+1} \leq \Gamma_t, \quad t = 1, \dots, T+1,$$

where Γ_t stands for the budget of uncertainty for the cost estimates of all project stages occurring in period t . The budget of uncertainty helps to avoid overconservatism by controlling the robustness of the constraint set (2) against level of conservatism.

Corollary.

The uncertain formulation (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), Model (1), Model (2), Model (3) and (11) has the following robust counterpart:

equation(Model 4)

$$\begin{aligned}
& \max (l_{T+1} - b_{T+1}) \\
& \text{s.t.} \\
& \sum_i \sum_{j=\max\{t_i^-, t-k_i\}}^{\min\{t, t_i^+\}} (\bar{c}_{it}^{t-j+1} x_{ij} + u_{it}^{t-j+1}) + l_t + b_{t-1}(1+r_{t-1}+\Delta) + \Gamma_t q_t \\
& \leq l_{t-1}(1+r_{t-1}) + b_t + \beta_t, \quad t = 1, \dots, T+1 \\
& q_t + u_{it}^{t-j+1} \geq \hat{c}_{it}^{t-j+1} y_{ij}, \quad i = 1, \dots, n; \quad t = 1, \dots, T+1; \\
& \max\{t_i^-, t-k_i\} \leq j \leq \min\{t, t_i^+\} \\
& \sum_{j=t_i^-}^{t_i^+} x_{ij} \leq 1, \quad i = 1, \dots, n \\
& \sum_i \sum_{j=\max\{t_i^-, t-k_i+1\}}^{\min\{t, t_i^+\}} r_{im}^{t-j+1} x_{ij} \leq R_t^m \quad \forall m; \quad t = 1, \dots, T \\
& x_{pt} \leq \sum_{j=t_i^-}^{\min\{t_i^+, t-k_i-g_p\}} x_{ij}, \quad (i, p) \in \Omega; \quad t = t_p^-, \dots, t_p^+ \\
& \sum_{j=t_i^-}^{t_i^+} x_{ij} = 1, \quad i \in \Theta^M \\
& x_{i1} = 1, \quad i \in \Theta^0 \\
& b_t \leq B, \quad t = 1, \dots, T \\
& -y_{ij} \leq x_{ij} \leq y_{ij}, \quad i = 1, \dots, n; \quad j = t_i^-, \dots, t_i^+ \\
& y_{ij} \geq 0, \quad i = 1, \dots, n; \quad j = t_i^-, \dots, t_i^+ \\
& x_{ij} \in (0, 1), \quad i = 1, \dots, n; \quad j = t_i^-, \dots, t_i^+ \\
& b_t, l_t \geq 0, \quad t = 1, \dots, T+1 \\
& q_t, u_{it}^{t-j+1} \geq 0, \quad i = 1, \dots, n; \quad t = 1, \dots, T+1; \\
& \max\{t_i^-, t-k_i\} \leq j \leq \min\{t, t_i^+\}.
\end{aligned}$$

Proof.

In the uncertain model (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), Model (1), Model (2), Model (3) and (11), variables x_{ij} are (binary) integers and variables l_t and b_t are continuous and bounded. Constraint (2) is the only constraint with uncertain parameters \hat{c}_{it} , and all other constraints as well as the objective function comprise deterministic parameters only. Noting that binary variable is a special case of integer variable, and also that in Bertsimas and Sim (2003) approach, the

deterministic objective function and deterministic constraints remain intact in transition to linear counterpart, Model (4) directly follows from derivation of Model (3) from Model (2).□

Model (4), called the RoCROP model, is a MILP problem which is of the same class as that of the nominal problem. Therefore, it has the characteristic of rapid re-optimization which helps evaluating the effect of budget of uncertainty changes to the optimal R&D project portfolio schedule.

5. An illustrative example of RoCROP model

In this section, we present the results of an illustrative example where the RoCROP model has been applied to a CRO portfolio. We borrow our main problem data from Rogers et al. (2002) where a pure project selection problem in pharmaceutical R&D is addressed. We next generate plausible and reasonable values for project-specific data (e.g., early and tardy start years, external budget availability, borrowing limit, project resource requirement, resource availabilities, and delayed development cost estimates) that were not included in Rogers et al. (2002) but are required for our problem setting. For this illustration, we also use our experience of working with a CRO to represent macroeconomic data such as the interest-free rate and the borrowing rate that are realistic and conform to the industry standards and macroeconomic norms.

The CRO currently faces 11 new drug development opportunities along four development phases. At the moment, the project portfolio consists of 5 projects beginning clinical phase II, 5 projects beginning phase III, and 4 projects beginning phase IV. The company needs to consider the new project opportunities for selection and scheduling. As before we assume that each project opportunity, upon selection, will be continually carried into completion. At the current revision period, however, we may need to postpone or even terminate some of the ongoing projects due to a variety of reasons, including the arrival of more promising projects, scarcity of resources required for further development, or the request of the client company. Upon completion of a project, the company receives the contract value from the client. It is intuitively apparent that projects with low investment costs, low resource consumption, and high contract values are generally preferable over others. Table 1 summarizes project data including phase durations, estimated development costs, contract values, and early and tardy start years imposed by contract terms. We use notation t_i^+ for contract-based tardy start year of project i presented in the last column of Table 1. Note that for projects 1-8 and 12-16 with no contract-based tardy start year, we assume a temporary value of infinity that will be contained later. For each year where a project phase is postponed beyond its early start year, the development costs increase by 1.5% to reflect the cost increase due to inflation. The contract value is highly dependent on project delivery time and is assumed to decline exponentially with rate of -0.10 per year delay above its early delivery time. These assumptions are made merely to simplify data presentation for the delayed costs and revenues. Using our notation in Section 3, time-dependent costs and contract values are respectively represented by the following equations:

equation(12)

$$c_{it}^k = c_{i, t_i^- + k - 1}^k \times 1.015^{t - t_i^- - k + 1}$$

equation(13)

$$c_{it}^{k_i+1} = c_{i, t_i^- + k_i}^{k_i+1} e^{-0.1(t - t_i^- - k_i)}.$$

Table 1. Phase lengths, costs, project contract values, and early and tardy start years for the 25 projects.

Project	Length (years) of phase				Cost of phase ^a				Contract value ^a	Early start year	Tardy start year
	I	II	III	IV	I	II	III	IV			
1	1	2	2	3	2	10	20	20	120	5	-
2	1	2	3	4	5	20	35	120	400	5	-
3	1	1	2	3	3	20	50	100	320	3	-
4	1	3	2	3	10	5	30	75	240	3	-
5	1	1	2	2	5	15	110	290	680	3	-
6	1	1	2	3	2	10	20	30	180	2	-
7	1	1	3	2	3	10	40	45	190	1	-
8	1	1	2	2	10	15	60	100	320	1	-
9	1	1	3	3	5	15	45	55	280	1	10
10	1	1	2	2	20	80	85	200	810	1	10
11	1	1	2	2	15	15	25	45	180	1	10
12		1	2	2		10	25	30	110	1	-
13		1	2	3		20	35	40	190	1	-
14		1	3	2		20	50	75	250	1	-
15		1	3	2		30	55	120	430	1	-

16		1	2	2		10	25	30	110	1	-
17			2	3			30	60	160	1	5
18			3	2			75	180	510	1	5
19			2	2			90	180	480	1	4
20			1	2			50	100	320	1	3
21			1	2			80	150	350	1	4
22				2				180	290	1	3
23				3				70	170	1	3
24				1				85	220	1	3
25				1				35	50	1	3

aEstimated in million dollars based on the early start year.

Currently, there is no liquidity in CRO's bank account. External budgets of 100 million dollars are available during the first 3 years. The liability limit is set to 400 million dollars. The annual risk-free interest rate and borrowing rate for the CRO in question are assumed to be 5% and 14%, respectively. The company maintains 150 specialists and 8 laboratories. Table 2 presents annual number of specialists and laboratory units required during the project phases.

Table 2. Annual resource consumptions for the 25 projects.

Project	Annual specialist requirement in phase				Annual laboratory requirement in phase			
	I	II	III	IV	I	II	III	IV
1	5	15	20	1	1	0.9	1.1	0.5
2	15	30	80	1	1.7	1	1.9	0
3	10	30	50	1	1.2	2.1	1.6	0
4	25	9	30	1	1.9	0.4	1.6	0
5	15	24	110	1	0.9	1.5	3.6	0
6	5	15	20	1	0.5	1.4	1	0

7	10	15	40	1	1	1.4	1.7	0
8	25	24	60	1	2.1	1.6	1.7	0
9	15	24	50	1	1.3	1.6	1	0
10	50	60	46	1	2.6	4	1.5	0
11	40	24	26	1	2.4	2.3	1.7	0
12		15	26	1		1.8	1.2	0
13		30	36	1		1.9	1.9	0
14		30	56	1		2.5	1.5	0
15		45	56	1		2.5	1.2	0
16		15	26	1		1.9	0.8	0
17			30	1			1.3	0
18			76	1			2.1	0
19			90	1			3.4	0
20			50	1			3	0
21			80	1			4.9	0
22				1				0
23				1				0
24				1				0
25				1				0

Table options

To tackle the problem, we first set project stages (periods) to years. As a result each project phase may span several stages (years), as depicted in Fig. 3.

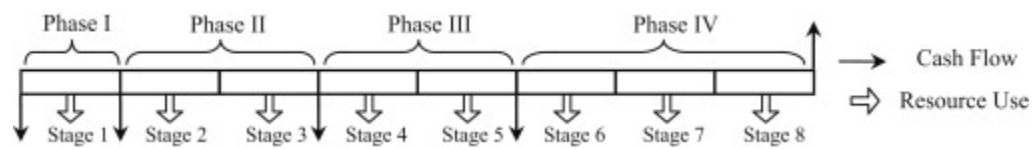


Fig. 3. Development pipeline for project 1.

Let $n=25$, $B = 400$, $r=5\%$, $\Delta=14\%-5\%=9\%$, and $\beta_t=100$ for $t=1,2,3$. Without loss of generality, we assume that development costs occur at the beginning of phases. For example, for project 1, we let $k_1=8$, $t_1^- = 5$, $c_{15}^1 = 2$, $c_{16}^2 = 10$, $c_{17}^3 = 0$, $c_{18}^4 = 20$, $c_{19}^5 = 0$, $c_{1,10}^6 = 20$, $c_{1,11}^7 = c_{1,12}^8 = 0$, and $c_{1,13}^9 = -120$, where cash flows for the postponed project are calculated from (12) and (13). For the specialist resource, we have $r_{11}^1 = 5$, $r_{11}^2 = r_{11}^3 = 15$, $r_{11}^4 = r_{11}^5 = 20$, $r_{11}^6 = r_{11}^7 = r_{11}^8 = 1$, $R_t^1 = R^1 = 150$, and for the laboratory resource, $r_{12}^1 = 1$, $r_{12}^2 = r_{12}^3 = 0.9$, $r_{12}^4 = r_{12}^5 = 1.1$, $r_{12}^6 = r_{12}^7 = r_{12}^8 = 0.5$, and $R_t^2 = R^2 = 8$.

In order to determine the appropriate planning horizon, we chose to use the net present value (NPV) method to shorten the planning horizon and reduce the number of decision variables. Note that the optimal solution may not involve projects that have negative NPV (the 25 projects meet this requirement if initiated at their early start year). Since costs and revenues are respectively increasing and decreasing functions of project start year, the NPV is a decreasing function of project start year (which is typical of almost all R&D projects) and hence, each project can be postponed up to a limited number of years to maintain its financial viability. This may impose earlier tardy start years than the contract-based tardy start years in Table 1. The NPV of project i initiated at period t is calculated by discounting costs and revenues to the beginning of the planning horizon as in the following:

equation(14)

$$NPV_{it} = - \sum_{k=1}^{k_i+1} \left(c_{i,t+k-1}^k \prod_{j=1}^{t+k-2} (1+r_j)^{-1} \right).$$

The tardy start year of project i can be calculated as $t_i^+ = \max \{t | t_i^- \leq t \leq t_i'^+, NPV_{it} > 0\}$. We next calculate the tardy start year of the 25 projects as 10, 9, 6, 7, 6, 9, 5, 4, 6, 6, 4, 4, 5, 4, 5, 4, 4, 5, 4, 3, 3, 3, 3, 3, and 3. The tardy completion year of project i occurs at the end of period $(t_i^+ + k_i - 1)$, which is calculated as 17, 18, 12, 15, 11, 15, 11, 9, 13, 11, 9, 8, 10, 9, 10, 8, 8, 9, 7, 5, 5, 4, 5, 3, 3 for the 25 projects, correspondingly. The planning horizon (T) is set to 18 years which is the maximum of all tardy completion years. As a result, the formulated model consists of 110 binary integer variables.

To solve the nominal model, we insert all problem data in an Excel Worksheet and use the Object Linking and Embedding automation link between LINGO and Excel to export problem data to LINGO. This is implemented on a PC workstation with a 500 MHz CPU and 256 MB physical memory. The model takes about 4 s to solve and the optimal objective is 3299.89. Fig. 4 shows the optimal project portfolio schedule for the nominal solution.

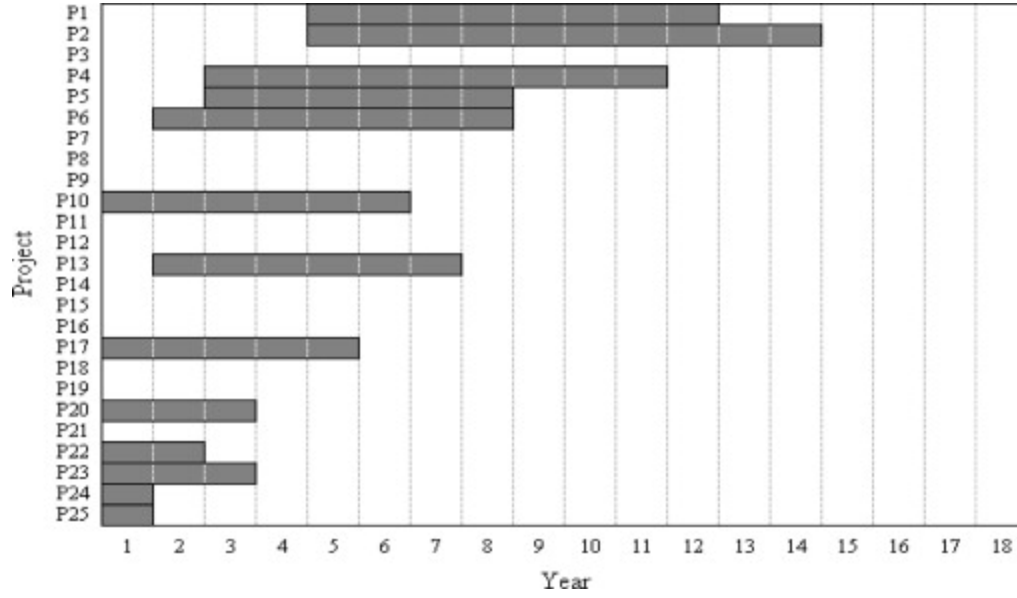


Fig. 4. Optimal project portfolio schedule for the nominal problem.

In order to analyze the effects of uncertainty, we assume that all cost estimates may deviate up to 20% around their nominal values, i.e., $\hat{c}_{it}^k = 0.2\bar{c}_{it}^k$. For the sake of simplicity, we also set all vector components Γ_t equal to Γ . We solve Model (4) for different values of Γ by increments of 0.1 units. Our numerical experiment shows that projects 8, 11, 14, 19, and 21 are never selected for any Γ value. The resulting project portfolio schedules with respect to Γ are summarized in Table 3.

Table 3. Optimal solutions obtained for various Γ values.

Solution	Γ	Start year of project																								Robust objective
		1	2	3	4	5	6	7	9	10	12	13	15	16	17	18	20	22	23	24	25					
S1	0.0 → 0.2	5	5		3	3	2			1		2			1		1	1	1	1	1		3299.89→ 3000.02			
S2	0.3 → 0.4	5	5		3	3	2			1		1					1	1	1	1	1		2847.43→ 2703.36			
S3	0.5	7	6	5	3	3	2			1		1					1	1	1	1	1		2559.25			
S4	0.6	7	6	5	3	3	2			1		1					1	2	1	1	1		2433.99			
S5	0.7 → 1.2	8	6	5	3	3	2			1		1					1	2	1	1	1		2313.57→ 1832.85			

S6	1.3	5	7	3	4		3		2					1		1	1	2	1	1	1	1782.69
S7	1.4 → 1.6	5	7	3	4		3		2		1					1	1	2	1	1	1	1738.31→ 1645.85
S8	1.7	5	7	3	4		3		2		1					1	1		1	1	1	1602.86
S9	1.8 → 2.0	5	7	3	4		3		2						2	1	1		1	1	1	1566.47→ 1494.7
S10	2.1 → 2.2	5	5	3	3		2	2								1	1		1	1	1	1471.68→ 1452.77
S11	2.3	5	5		4		2		1							1	1		1	1	1	1434.49
S12	2.4 → 2.9	5	5		3		2		1	1							1		1	1	1	1420.29→ 1352.18
S13	3→ 4.2	5	5		3		2		1				1				1		1	1	1	1339.27→ 1274.4
S14	4.3 → 25	5	5		3		2		1				1				1		1	1		1269.91

It is intuitive that the robust objective is always a decreasing function of Γ . Therefore, in order to be consistent with the deterministic case and be able to fairly analyze the performance of robust solutions, we calculate deterministic objective values by substituting the 14 robust solutions of Table 3 in the nominal model and computing corresponding objective functions. In addition, in order to analyze robustness of the solutions, Monte Carlo simulation is performed by randomly drawing c_{it}^k from the range of possible values that may adversely affect the objective function and substituting the robust solutions in the model to compute the probability of violating solution feasibility. A total of 1000 sets of randomly selected coefficient values are generated. We also compute the optimal objective function for any given realization of simulated parameters and compare it with the objective function of the robust solution to calculate the average regret. The results are summarized in Table 4. From this table, the nominal solution has very small feasibility chance (11.3%). This clearly demonstrates that the nominal project portfolio schedule is a very risky decision. Based on the two middle columns of Table 4, we identify S1, S2, S4, and S12 as the non-dominated solutions.

Table 4. Analysis of robustness of solutions.

Solution	Deterministic objective (%)	Probability of feasibility (%)	Average regret (%)
S1	3299.89 (100%)	11.3	6.8
S2	3261.93 (98.8%)	31.4	6.0
S3	3231.95 (97.9%)	31.4	9.8
S4	3150.96 (95.5%)	46.0	13.1
S5	3137.19 (95.1%)	46.0	13.6
S6	2715.51 (82.3%)	100.0	19.3
S7	2715.51 (82.3%)	100.0	19.3
S8	2652.22 (80.4%)	100.0	16.8
S9	2655.36 (80.5%)	100.0	17.1
S10	2707.97 (82.1%)	100.0	12.8
S11	2620.74 (79.4%)	100.0	14.3
S12	2890.93 (87.6%)	100.0	7.5
S13	2598.86 (78.8%)	100.0	14.4
S14	2573.73 (78.0%)	100.0	14.5

For practical purposes, note that S1 may be replaced by S2 that has better worst-case performance ($\Gamma=0.4$ versus $\Gamma=0.2$), higher feasibility chance (31.4% versus 11.3%), and better average regret performance (6.0% versus 6.8%). In the same way, S4 may be replaced by S12. In addition S12 has better worst-case performance and much higher feasibility chance than that of S2, whereas its average-regret performance is merely 1.5% higher than that of S2. Therefore, one might consider S12 as the best practice. The S12 portfolio consists of projects 1, 2, 4, 6, 9, 10, 20, 23, 24, and 25, the schedule of which is depicted in Fig. 5.

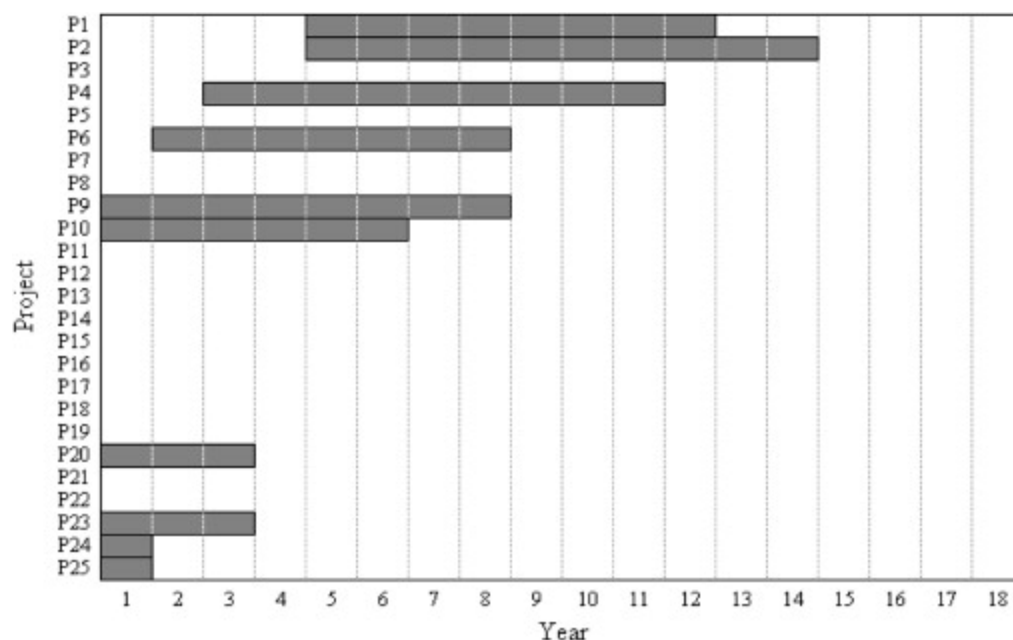


Fig. 5. The best practice for robust portfolio schedule (S12).

6. Conclusions

This paper develops a robust model to assist CROs in making their primary business decision, i.e. selection and scheduling of new drug development project opportunities. We considered financial transactions of CRO as well as resource and several other technical concerns associated with drug development projects and formulated a mathematical model that captured the parameters of the decision making environment. The developed tool incorporates incomplete information about pharmaceutical R&D cost and revenue estimates into the model by capturing uncertainty as interval of possible values. The adopted robust optimization approach generated solution alternatives that were filtered by a Monte Carlo simulation for the final consideration. The approach is very convenient from managerial standpoint because it requires only crude financial estimates to implement. This is in contrast with stochastic or fuzzy optimization methods where distributional information is required to make a decision, a requirement which is highly undesirable if not impractical in pharmaceutical R&D setting. In addition, our approach handles uncertainty *ex-ante* and provides decision alternatives that have different performance and robustness degrees. This is in contrast to the conventional sensitivity analysis that is *ex-post* and merely measures the sensitivity of the single suggested solution to small variations in parameters without providing a method to mitigate this sensitivity and improve the decision.

The framework developed in this paper targets enhancement of decision making from a CRO perspective. CROs maintain a pipeline of projects from various clients and periodically consider new requests from pharmaceutical companies and add them to their pipeline according to their convenience. In a similar manner, pharmaceutical companies identify new or incrementally-improved drug molecules and consider adding them to the portfolio of their own drugs. As a

result, this framework can also assist pharmaceutical companies in making R&D decisions. In addition, organizations that plan and execute generic risky projects within private sector (food, technology, software, construction, oil and mining) and public sector (governmental, municipal, environmental, tourism, national security and defense projects) can also benefit from this framework.

The proposed model should prove invaluable for all CROs, especially those with a big client base and considerably large R&D portfolio sizes. We, however, do not suggest that our approach captures all the complexities involved in the pharmaceutical R&D PSS such as synergistic interplay among drug projects, uncertainty in length of clinical phases, and the decision maker's preferences. As a future research direction, we also suggest that the more effective real options value as well as the technical success chance of project phases be incorporated into the PSS framework.

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